Complete Summary

GUIDELINE TITLE

The role of oxaliplatin combined with 5-fluorouracil and folinic acid in the first and second-line treatment of advanced colorectal cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Jonker D, Rumble RB, Maroun J, Gastrointestinal Cancer Disease Site Group. The role of oxaliplatin combined with 5-fluorouracil and folinic acid in the first and second-line treatment of advanced colorectal cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Dec 8. 33 p. (Evidence-based series; no. 2-22). [15 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Advanced (non-resectable locally advanced or metastatic) colorectal cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Gastroenterology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of oxaliplatin combined with 5-fluorouracil (5-FU) and folinic acid (FA) in the first- and second-line treatment of advanced (non-resectable locally advanced or metastatic) colorectal cancer

TARGET POPULATION

Adult patients with advanced colorectal cancer who have high performance status (Eastern Cooperative Oncology Group [ECOG] 0-2)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Oxaliplatin combined with 5-fluorouracil (5FU) and folinic acid (FA) (FOLFOX) in first and second-line therapy
2. FOLFOX combined with bevacizumab

MAJOR OUTCOMES CONSIDERED

- One-year survival
- Response rates
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

MEDLINE (1966 to June [week 1] 2006), CANCERLIT (1975 to October 2002), EMBASE (week 26 2003 to week 23 2006), Guidelines International Network

(http://www.guidelines-international.net/), and the Cochrane Library (Issue 1, 2006) were searched. The Medical Subject Heading [MeSH] search terms "colonic neoplasms," "rectal neoplasms," and "colorectal neoplasms" were combined with the text words "oxaliplatin," "L-OHP," "LOHP," and "FOLFOX." These results were then combined with the following terms describing specific study designs: "random" and "clinical trial". Results were limited to the English language. The conference proceedings of the 1999 to 2006 annual meetings of the American Society of Clinical Oncology (ASCO), including the 2004 through 2006 Gastrointestinal Cancer Symposiums, were also searched for reports of new or on-going trials. The reference lists from retrieved papers were searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were:

1. Phase III randomized controlled trials (RCTs) of oxaliplatin (L-OHP) combined with 5-fluorouracil (5FU)/folinic acid (FA) or capecitabine as first-line or second-line therapy for advanced colorectal cancer.
2. Full publications or abstract reports of trials.
3. English-language published reports.

NUMBER OF SOURCE DOCUMENTS

The literature search found thirty-three reports, including twenty-seven reports of randomized controlled trials (RCTs) of first-line treatment involving sixteen separate RCTs, two meta-analyses on first-line treatment, and four reports on second-line treatment.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

For the following reasons, the Gastrointestinal Cancer Disease Site Group (DSG) decided not to pool the results of the trials found in the literature search:

- Treatments described were too heterogeneous to allow for pooling.

- Evidence from the studies obtained provided a clear indication of benefit or harm.
- Published meta-analyses of individual patient data were available. (The meta-analyses are discussed in the appropriate sections of the original guideline document).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This evidence-based series was developed by the Gastrointestinal Cancer Disease Site Group (DSG) of Cancer Care Ontario's (CCO's) Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on oxaliplatin (L-OHP) combined with 5-fluorouracil (5-FU) and folinic acid (FA) in advanced colorectal cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Disease Site Group Consensus Process

Note: The Gastrointestinal DSG consensus process was based on an earlier draft of the present guideline document. That draft did not contain any of the evidence regarding the addition of bevacizumab to regimens of infusional 5FU/FA plus oxaliplatin.

The present systematic review found one first-line therapy trial that demonstrated infusional 5FU/FA/oxaliplatin (FOLFOX) to be superior to bolus 5FU/FA/irinotecan (IFL), with more-favourable median survival and tumour response rates. Compared with IFL, FOLFOX has lower incidences of severe nausea, vomiting, diarrhea, and febrile neutropenia, but a higher incidence of peripheral neuropathy. Therefore, for first-line treatment, short-term infusional 5FU/FA in combination with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) is acceptable for fit patients when combination therapy is the preferred treatment. Choice of first-line therapy may rely on patient factors and preferences—for example, less neuropathy with irinotecan versus less alopecia with oxaliplatin.

For second-line treatment after progression on first-line anti-thymidylate synthase (TS) monotherapy (for example, 5FU/FA, capecitabine), irinotecan is standard therapy. For patients with contraindications to the use of second-line irinotecan, FOLFOX is a reasonable alternative. After progression on both irinotecan and an anti-TS agent, FOLFOX is the preferred therapy.

The role of radiation therapy, either alone or in combination with chemotherapy, for locally advanced unresectable colorectal cancer was not addressed in this guideline. In addition, the use of chronomodulated (CM) regimens is a topic that intersects with the use of oxaliplatin/5FU combinations, particularly CM 5FU in those combinations. Chronomodulation of oxaliplatin has not been extensively studied and was not addressed, because the topic is beyond the scope of this guideline.

In conclusion, the Gastrointestinal DSG acknowledges that the combination of oxaliplatin with short-term infusional 5FU and FA (FOLFOX) is an important component of first- and second-line treatment of advanced colon cancer, and the DSG recommends that oxaliplatin be made available for the treatment of advanced colorectal cancer.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External Review by Ontario Clinicians

Following review and discussion of sections 1 and 2 of this evidence-based series, the Gastrointestinal Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Practitioner feedback was obtained through a mailed survey of 63 practitioners in Ontario (11 medical oncologists, nine radiation oncologists, and 42 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on September 15, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gastrointestinal Cancer DSG reviewed the results of the survey.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Refer to Appendix 1 in Section 2 of the original guideline document for recommended dosages and schedules.

Combination oxaliplatin, short-term infusional 5-fluorouracil (5FU), and folinic acid (FA) (FOLFOX) is an important component of therapy, and oxaliplatin should be made available for the treatment of advanced colorectal cancer.

First-line Therapy

- FOLFOX was shown to be superior to bolus 5FU/FA/irinotecan (IFL) in one trial. The FOLFOX regimen has superior median survival and tumour response rates. Compared with IFL, FOLFOX has lower incidences of severe nausea, vomiting, diarrhea, and febrile neutropenia, but higher peripheral neuropathy.
- Short-term infusional 5FU/FA in combination with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) are both acceptable alternatives for fit patients when combination therapy is the preferred treatment. Choice of first-line therapy may rely on patient factors and preferences, for example, less neuropathy with irinotecan versus less alopecia with oxaliplatin.

Second-line Therapy

- After progression on first-line anti-thymidylate synthase monotherapy (e.g., 5FU/FA; capecitabine), irinotecan is the standard second-line therapy. FOLFOX is a reasonable alternative for patients with contraindications to the use of second-line irinotecan.
- After progression on both irinotecan and an anti-thymidylate synthase agent, FOLFOX is the preferred therapy. Recent trials suggest that, as compared to FOLFOX alone, FOLFOX combined with bevacizumab provides additional survival benefits.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials (RCTs) and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

First-line Therapy

- Four fully published studies have compared combination 5-fluorouracil/folinic acid (5FU/FA)/oxaliplatin with combination 5FU/FA/irinotecan. The largest of these studies, performed by the U.S/Canadian Intergroup, compared the infusional 5FU/FA/oxaliplatin (FOLFOX) regimen to the bolus 5FU/FA/irinotecan (IFL) regimen. This study demonstrated a 4.5 month improvement in median survival (15 months versus 19.5 months) favouring the infusional FOLFOX regimen. Although this evidence suggests the superiority of oxaliplatin/5FU combinations over irinotecan combinations, there is further evidence to suggest that the superiority of FOLFOX in this study is related to its use within an infusional 5FU regimen. Three studies compared oxaliplatin-based and irinotecan-based regimens where 5FU was delivered in an identical fashion. The study comparing FOLFOX vs. infusional

5FU/FA/irinotecan [FOLFIRI] did not detect any differences between treatments. Results of the Southern Italy Cooperative Oncology Group (SICOG) 0103 trial (comparing oxaliplatin, folinic acid, 5FU [OXAFAFU] vs. irinotecan, folinic acid, 5FU [IRIFAFU]) detect a significant benefit for OXAFAFU in one-year overall survival (39% vs. 23%; p=0.032). The results of the Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) study, a crossover study using short-term infusional 5FU in both treatment arms, were reported. That trial compared FOLFOX followed (at the time of progression) by FOLFIRI versus FOLFIRI followed by FOLFOX. The study demonstrated similar median survival (21.5 months versus 20.6 months) and overall response rate (56% versus 54%) in first-line treatment. FOLFOX was associated with lower 60-day mortality, a lower incidence of severe nausea, less vomiting, less diarrhea, and less febrile neutropenia, but was associated with a higher incidence of peripheral neuropathy.

- Four trials have compared first-line combination 5FU/FA/oxaliplatin to 5FU/FA alone. Only two of these trials reported one-year survival outcomes, and no difference was detected in either trial. However, all three of the trials that reported on overall response rate detected a superior benefit favouring the addition of oxaliplatin to 5FU/FA.
- A meta-analysis of seven randomized controlled trials (RCTs) involving 3,186 patients comparing combination chemotherapy (either oxaliplatin or irinotecan in combination with 5FU) with 5FU-based therapy alone detected a significant 3.5 month increase in median survival (p=0.0083) in patients who received a first-line combination therapy (either oxaliplatin/5FU/FA or irinotecan/5FU/FA).
- Three trials have examined chronomodulated (CM) 5FU in combination with oxaliplatin versus fixed-rate 5FU in combination with oxaliplatin. A pooled analysis of the seven-year results of two underpowered trials (abstract only) demonstrated superior overall response rate (ORR%) (51% versus 30%; p<0.001), complete surgical resection (23.3% versus 12.8%; p<0.001), and median progression-free survival (PFS) (10.3 versus 7.5; p=0.039) favouring chronomodulated therapy, without a difference in median survival (18.6 versus 16.5 months; p=0.22) or survival at either 5 or 7 years (5year: 12.6 versus 15.2; 7year: 6.6 vs. 7.1). A third trial reported no significant difference in overall survival or progression-free survival between treatment groups.

Second-line Therapy

- The ECF4584 trial demonstrated improvements in time to progression and response rate with second-line FOLFOX compared to oxaliplatin alone or infusional 5FU/FA alone in patients who progressed on the irinotecan, leucovorin calcium, bolus 5FU (ILF) regimen. Combination 5FU/FA/oxaliplatin is an acceptable palliative therapy in patients who have progressed on both 5FU/FA/irinotecan. Presently, there remains more evidence supporting second-line irinotecan than 5FU/FA/oxaliplatin or oxaliplatin alone, but oxaliplatin in combination with infusional 5FU/FA is a reasonable alternative for patients considered poor candidates (Eastern Cooperative Oncology Group [ECOG] 3-4) for second-line irinotecan. Interim analysis of that trial detected an overall symptom relief difference favouring treatment with FOLFOX4 (33% versus 12%).

- One study reported a significant improvement in the median time to progression (4.9 months vs. 2.6 months) and objective response rate (11.1% vs. 1.9%), favouring FOLFOX over 5FU/FA.
- Another study reported a significant benefit in the objective response rate, favouring the sequence FOLFOX4 followed by CPT-11 over CPT-11 followed by FOLFOX4 (27% vs. 15%, $p<0.0142$).
- A study reported in abstract form compared FOLFOX4 with and without bevacizumab and found that the addition of bevacizumab to the FOLFOX regimen resulted in significant gains in both median survival (10.7 months vs. 10.2 months, $p=0.0024$) and progression-free survival (7.4 months vs. 5.5 months, $p=0.0003$).

POTENTIAL HARMS

First-line treatment with oxaliplatin is associated with significantly more peripheral/sensory neuropathy and neutropenia in addition to any adverse effects expected from any other drug given in the regimen.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The role of radiation therapy, either alone or in combination with chemotherapy, for locally advanced non-resectable colorectal cancer is not addressed in this guideline.
- Use of chronomodulated regimens is a topic which intersects with the use of oxaliplatin/5-fluorouracil (5FU) combinations, particularly chronomodulation of 5FU in these combinations. Chronomodulation of oxaliplatin has not been extensively studied, and the topic of chronomodulation is beyond the scope of this guideline and will not be thoroughly addressed.
- Although data exist to support the use of bevacizumab in combination with 5-fluorouracil/folinic acid/oxaliplatin (FOLFOX) in second-line treatment, no first-line treatment data are available on which to make a recommendation.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Jonker D, Rumble RB, Maroun J, Gastrointestinal Cancer Disease Site Group. The role of oxaliplatin combined with 5-fluorouracil and folinic acid in the first and second-line treatment of advanced colorectal cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Dec 8. 33 p. (Evidence-based series; no. 2-22). [15 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 (revised 2006 Dec)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Gastrointestinal Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Gastrointestinal Cancer Disease Site Group (DSG) disclosed potential conflicts of interest relating to the topic of this practice guideline. Two of the guideline authors reported no conflicts of interest. One of the guideline authors reported research involvement with the pharmaceutical company that manufactures the chemotherapy agent recommended in this guideline. No other Gastrointestinal Cancer Disease Site Group member declared any conflicts with respect to this report.

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on December 1, 2006. The information was verified by the guideline developer on January 19, 2007. This summary was updated by ECRI Institute on April 9, 2008.

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